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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: X. Nair et al **Group Art Unit:** ~~125~~ 152.
Serial No.: 554,904
Filed : 07/24/90
For : Synergistic Skin Depigmentation Composition

#2 D. Gassaway 9-12-90

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

INFORMATION DISCLOSURE STATEMENT BY APPLICANTS UNDER MPEP 707.05 (b)

In accordance with the guideline set forth in MPEP 707.05(b) for the submission of relevant art by applicant, his attorneys and agents to the Patent Office for consideration, please find below citations of such art. Full text copies (or in some cases, abstracts) of such are not enclosed because they have been made of record in parent case Serial No. 397,291 filed 8/24/89. Applicant respectfully requests that this letter be made of record.

CITATION OF ART

This invention relates to a synergistic skin depigmentation composition comprising 4-hydroxyanisole and a retinoid such as all-trans retinoic acid, 11-cis,13-cis-12-hydroxymethyl retinoic acid δ-lactone or (N-acetyl-4-amino-phenyl) retinoate.

4-Hydroxyanisole is present as the active ingredient in products used topically for depigmenting or lightening of skin. These products are used in the treatment of hyperpigmentation of skin associated with various skin disorders or diseases. The hyperpigmentation is generally the result of increased melanin deposition in epidermal cells. Hyperpigmentation of skin is associated with

freckles, senile lentigo, lentigines, melasma, post-inflammatory hyperpigmentation, sunburn, phototoxic reactions and other conditions. In general, these cases of hyperpigmentation are not life-threatening, but are viewed as cosmetically undesirable and psychologically debilitating.

Local side effects are often associated with the existing products containing greater than 2% hydroquinone or 4-hydroxyanisole. These side effects include localized irritation and irreversible depigmentation. Products containing 2% or less of hydroquinone or 4-hydroxyanisole are generally regarded as ineffective in the treatment of lentigo or melasma.

All-trans retinoic acid (vitamin A acid) applied topically has been reported to lighten the color of lentigo in humans. All-trans retinoic acid is known to increase epidermal cell turnover in normal skin and suppress epidermal cell turnover under stimulated or hyperproliferative conditions. It causes epidermal keratinization and decreases the number of normal cell layers of the stratum corneum. This decrease in thickness of the barrier may potentiate the penetration of other topical agents.

U.S. Patent No. 3,856,934 and Canadian Patent No. 982,945 disclose a synergistic composition for depigmentation of skin comprising a mixture of hydroquinone, retinoic acid, and a corticosteroid. The U.S. patent also discloses that the double combination of hydroquinone and retinoic acid was not synergistic. Therefore, all three components were needed for the synergistic activity. The Canadian patent discloses that hydroquinone monomethyl ether (4-hydroxyanisole) may be used in the composition instead of

hydroquinone. In these patents the corticosteroid is regarded as necessary to bring irritation down to acceptable levels. However, the use of a corticosteroid possesses some disadvantages, i.e., it can be dangerous to use in intertriginous regions, and it may cause skin atrophy, rebound phenomenon and telangiectasia.

Respectfully submitted,

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DMM:jr